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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,788	01/06/2000	THOMAS JOHN BALDWIN	5673-53922	1383

7590 11/22/2004

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EXAMINER	
GRASER, JENNIFER E	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 11/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/445,788	BALDWIN ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,26,28-43 and 45* is/are pending in the application.

4a) Of the above claim(s) *28-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,26 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted on 9/3/04 is made. Claims 25, 26, and 45 are currently under examination.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 25, 26, and 45 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25 and 26 are vague and indefinite because of the phrase "using the native fur in the presence of low levels of ferric iron" in the last line of the claim. It is unclear what is meant by the term "native fur". Do Applicants mean the 'native fur promoter"? The claim should distinguish between the use of the modified gene promoter and the native promoter. Appropriated clarification and correction is required.

The wording of claim 45 is vague and confusing, e.g., to stimulate an immune response against the mutant bacterium, which is human or non-human animal, said method comprising vaccinating said subject with the vaccine composition of claim 25 thereby to stimulate an immune response against said bacterium. The claim should be amended so that the word "subject" in line 1 is replaced with "human or non-human animal" and 'which is a human or non-human animal' is deleted from line 2 of the claim.

Additionally, the word "the" before mutant in line 2 should be changed to "a" for proper antecedent basis. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 25, 26, and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "a vaccine composition comprising an attenuated live *Neisseria* bacterium having a genome wherein a native ferric uptake regulation (fur) gene promoter has substituted with *lacZ*promoter/*lacI* repressor whereby expression of a gene product corresponding to said fur gene is regulated independently of the iron concentration in the environment of the bacterium such that levels of expression of the modified fur gene are at least equal to those obtained using the native fur promoter in the presence of low levels of ferric ion; and a pharmaceutically acceptable carrier", does not reasonably provide enablement for "a vaccine comprising *any* attenuated live bacterium with *any* fur gene promoter deletion, insertion or substitution mutation, repressor whereby expression of a gene product corresponding to said fur gene is regulated independently of the iron concentration in the environment of the bacterium such that levels of expression of the modified fur gene are at least equal to those obtained using the native fur promoter in the presence of low levels of ferric ion; and a pharmaceutically acceptable carrier". The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification has demonstrated that be altering the regulation of the ferric uptake regulation (fur) gene in *N.meningitidis* by replacing the fur gene promoter with a *lacZ*promoter/*lacI* repressor, allows for expression independent of the iron concentration in the environment of the bacterium, thereby enhancing the expression of important protective antigens when the bacterium is grown in culture. The resulting low levels of the fur protein would enable the negatively regulated fur-controlled genes to be switched on, mimicking iron restricted conditions. Therefore, the attenuated bacterium with this mutation would still be able to fully express all iron-regulated proteins without the need for iron-restricted conditions thereby allowing the host to mount an immune response that would mimic that in response to the wild-type bacterium. It is taught that inactivation of the fur gene, itself, is often lethal to the bacterium since some fur expression appears to be required for positive regulation of some essential genes in *Neisseria*. By using the *lacZ*promoter/*lacI* repressor, positive regulation of galactosidase in the presence of lactose occurs which provides for sufficient production of fur to allow expression of essential genes and allows the control of fur expression to be regulated in response to intracellular lactose concentration. Since the *lac* inducer dissociates from the *lac* operator in the presence of lactose, fur expression can be reduced down to basal levels by growing the strain in the absence of lactose. In the absence of lactose, the bacteria will respond if as they are experiencing iron restricted

conditions, producing iron regulated proteins normally expressed *in vivo,* without the large use of iron chelators.

However, the specification fails to teach and provide an enabling disclosure for using other Genus of bacterium. The specification hypothesizes that other bacterium possess the same ferric uptake regulation system. However, it does not provide any examples which demonstrate mutating the promoters responsible for ferric uptake regulation in these other bacteria. Only a broad general statement that other bacterium, including but not limited to *Helicobacter pylori, Salmonella typhi, Salmonella typhirmurium* or *E.coli,* may have a homologous fur system which could be similarly mutated is provided. The specification does not enable the use of any bacterium except *Neisseria spp.* Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." The instant specification does not enable one of skill in the art to practice the claimed invention with a Genus of bacterium

other than *Neisseria*. The work involved would not be mere routine experimentation, but would require undue experimentation coupled with innovation.

The prior art teaches that the menigococcal *fur* gene is the most divergent of bacterium which possess it and that it appears to be essential in the N.meningitidis species. See Thomas et al (Mol.Microb. 1994.11(4):725-737). There is a great divergence in the fur system in different bacterial species. For instance, knocking out the entire fur gene in *Neisseria* would be fatal to the bacteria. Thomas et al demonstrate that mutations in the promoter of *E.*coli and *N.*meningitidis fur gene cause the bacterium to behave differently in the presence of iron. See page 728, column 2-page 729, column 1. Thomas also teaches that while at the level of DNA comparisons, *E.coli fur, V.cholera fur,* and *Y.pestis* fur, *N.meningitidis* fur is less closely related. Accordingly, it is unclear that the mutation taught in the *Neisseria* examples in the specification would behave similarly in other Genus of bacteria, e.g., that the enhancement of protective antigens seen in *Neisseria* would also occur in these other bacteria. It is noted that the instant specification provides only broad prophetic examples, other than use of the *lac*Zpromoter/*lacI* repressor in *Neisseria*, of how to mutate the fur gene promoter in order to obtain the desired result. Further, no results are shown to demonstrate that any of these prophetic constructs will have success as a vaccine. The bacterial vaccine art is highly unpredictable. A good immune response is not directly correlated to a *protective* immune response. Additionally, it is unclear how the *fur* gene promoter, with the exception of the *lac*Zpromoter/*lacI* repressor, can be modified so that it is regulated independent of the iron concentration in the environment

and so that the bacterium will still express essential genes and allow for enhancement of important immunoprotective antigens. It is unclear that all of the different modifications which are possible to allow for the *fur* gene promoter, e.g., any deletions, substitutions or additions, to be regulated independent of the iron concentration in the environment would provide an attenuated bacterium which would be successful as a vaccine. It is also noted that deletion of the *fur* gene promoter as encompassed by the claim would be lethal to the bacterium and, therefore, the bacterium would not be live and attenuated as required by the invention and claims. No results are provided with the various different mutants recited in the specification and their effectiveness as vaccines. Further, the specification only provides a discussion of possible modifications to be made and they are directed to solely *N.meningitidis*. These are only prophetic examples. No results are shown to demonstrate that any of these prophetic constructs will have success as a vaccine. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the

invention." That requirement has not been met in this specification. The specification is non-enabling, since one skilled in the art would not be able to make and use those sequences without undue experimentation.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomas et al (Mol.Microb. 1994.11(4):725-737).

Thomas et al teach a meningococcal fur gene transformed into an *E.coli* fur mutant with a *fur*-regulated *lacZ* fusion integrated into its chromosome. See page 728, column 2. Thomas et al also using different promoters to produce *E.coli* and *N.meningitidis* iron-responsive reporter systems. These systems use different or fused promoters to regulated the fur gene. See page 729, column 1. It is taught that the meningococcal *fur* construct showed regulatory activity on two single copy *E.coli* iron regulated promoters as well as in a multi-copy reporter system using either a neisserial iron-regulated promoter or another *E.coli* iron-regulated promoter, e.g., the modification of a native fur gene promoter by substitution. The strains used by Thomas et al are attenuated strains. The term "vaccine" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed

invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the preparation of the mutants. Additionally, the limitation "such that levels of expression of the modified fur are at least equal to those obtained using the native fur in the presence of low levels of ferric ions" would inherently occur in the mutants taught by Thomas since the structures are identical to the mutants instantly claimed.

Status of Claims

7. No claims are allowed. The former 35 U.S.C. 102(b) rejection of claims 25-27 and 45 as being anticipated by Allan et al (WO 94/05326) was overcome by the amendments to the claim because Allan taught a mutation in the *fur* gene, not the *fur* promoter as now required by the claims.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 872-9306 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

Jennifer Graser
Primary Examiner
Art Unit 1645

11/18/04